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Originalarbeiten

Dependence of Pulmonary Absorption Kinetics on Aerosol Particle Size[1])

Abhängigkeit der pulmonalen Absorptionskinetik von der Größe der Aerosol-Teilchen

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Zusammenfassung

Zur Ermittlung des Einflusses der Partikelgröße eines Aerosols auf die Absorption aus dem Atmungstrakt wurden polydisperse Dinatrium-Fluoreszeinaerosole (MMD_{ae} 1,1, 3,5 und 4,4 μm aus festem Aggregatzustand) erzeugt und unter gleichbleibenden Beatmungsbedingungen 2 Beagle-Hunden mit Überdruckbeatmung mit einer speziell für diesen Zweck geschaffenen Apparatur appliziert. Nach erfolgter Applikation wurde die Menge des absorbierten Fluoreszein an Hand des Plasmakonzentrationsverlaufes ermittelt und mit einer Modifikation der Methode von Loo Riegelmann ausgewertet. Eine maximale Deponierung im Atemtrakt wurde mit dem 3,5-μm-Aerosol erzielt. Fluoreszein wurde schnell aus dem Atemtrakt in einer Reaktion 1. Ordnung absorbiert. Die Absorptionsratenkonstante war unabhängig von der Partikelgröße und möglicherweise auch vom Ort der Deponierung. Die durchschnittlichen Halbwertszeiten der Absorption betrugen bei den beiden Hunden 17,3 und 11,4 Minuten.

Deskriptoren: Atemtrakt – Aerosolinhalation – Apparatur – Fluoreszein-Natrium – Absorption – Geschwindigkeitskonstante

Summary

To determine the effect of aerosol particle size upon absorption from the respiratory tract (RT), solid, polydisperse disodium fluorescein aerosols (MMD_{ae} 1.1, 3.5 and 4.4 μm) were delivered under the same respiratory regime direct to the RT of 2 Beagle dogs by positive pressure ventilation using a purpose designed administration system. Subsequent to aerosol administration the amount of fluorescein absorbed as a function of time was estimated from plasma concentration versus time and intravenous control data using a modified Loo Riegelman method. Maximum fractional deposition within the RT occurred with 3.5 μm aerosol. Fluorescein was absorbed rapidly from the RT according to an apparent first-order process the rate constant for which was independent of particle size and possibly regional deposition. Average values for absorption half lives in the 2 dogs were 17.3 and 11.4 minutes.

Key words: Respiratory Tract – Inhalation Aerosols – Aerosol Administration System – Disodium Fluorescein – Pulmonary Absorption – Absorption Rate Constant

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Introduction

The major uses of inhalation aerosols in medicine are a) for local administration of drugs to the respiratory tract for prophylactic and therapeutic control of bronchial asthma and b) clinical diagnosis of pulmonary disorders. Most diagnostic aerosols consist of water-insoluble radiolabeled particles, used to assess chronic obstructive airways disease (Agnew et al., 1981) or mucociliary clearance rates (Pavia et al., 1980). However, recent studies (Huchon et al., 1981; Jones et al., 1983) have indicated that soluble radiolabelled diagnostic aerosols may also be used to determine changes in pulmonary epithelial permeability with a view to predicting, and thus preventing, the onset of oedema associated with many pulmonary disorders.

Despite the advantages offered by the large absorptive area of the respiratory tract (Hatch and Gross, 1964) with few exceptions eg. Ergotamine aerosol Inhalation (1979) the use of inhalation aerosols for drug delivery to the systemic circulation has not been exploited. This probably reflects dosimetry difficulties associated with this type of drug delivery.

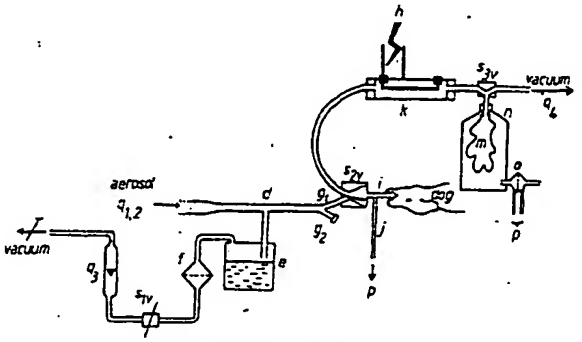
By studying the uptake of a variety of compounds delivered as intratracheal instillations to the mammalian repiratory tract, Schanker and co-workers [4, 12, 22, 27] found that one of the most significant factors effecting the rate at which a solute is transfered from the airways to the vasculature is its partition coefficient. They showed that, in comparison to lipophobic solute transport, which is confined primarily to extracellular routes, transcellular transport of lipophilic solutes was rapid. A compound presented as an inhalation aerosol cannot be absorbed unless it is first deposited in the respiratory tract. Total and regional deposition of inhaled particles within the respiratory tract are known to be functions of aerosol particulate characteristics [16, 17, 23, 28] and respiratory variables [25]. In order study the effect of some of these factors upon the deposition and absorption of drugs presented as inhalation aerosols, a system was designed [6] to deliver aerosols under a variety of controlled respiratory regimes to the Beagle. The present communication describes the way in which this system was used to determine the effect of aerosol particle size upon the absorption of a marker compound, fluorescein, delivered as a variety of aerosols of its disodium salt, under the same respiratory regime to 2 Beagle dogs. Subsequent to aerosol administration pulmonary absorption rates were determined by pharmacokinetic techniques [6]. Previous studies [7] have shown that following intratracheal instillation of a solution of its disodium salt, fluorescein is totally available for absorption from the canine respiratory tract.

Materials and Methods

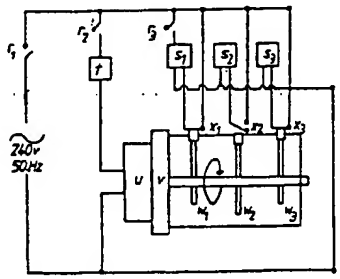
Apparatus. Fig. 1 is a diagrammatic illustration of the aerosol administration system employed, together with its valve control electronics. The operation of the system is described in the legend to this figure. The system was originally designed [6] for use in conjunction with a fluidised bed aerosol generator (Model 3400 Fluidised Bed Aerosol Generator, Thermo Systems Inc., St. Paul, Minnesota/USA) which manufactures dry aerosol but has since been used with a constant output

Fig. 1 Diagrammatic representation of the apparatus designed to ventilate and administer aerosols to the dog. The electronic circuit concerned with controlling the valves in this system is also shown.

Key: d = glass tubing with symmetrical ports, g_1 and g_2 for aerosol administration and sampling respectively and a port for removal of aerosol, e = water trap, f = filter, h = high voltage power supply unit, i = endotracheal tube, j = pressure line, k = electrostatic precipitator, m = elastic balloon, n = 2 litre bell jar, o = pneumotachograph flow head, p = combined pres-



Administration System



Valve Control Electronics

sure transducer and flow monitor, $q_{1,2}$, q_3 and q_4 = flow rates, S_1v = 2 way solonoid valve, S_2v = solonoid operated inspiration/expiration separator flap valve, S_3v = 3 way solonoid valve. Valve control electronics: t = electronic time delay unit, u = constant speed motor, v = stepping gears. $r_{1,2,3}$ = manual 2 way switches (subscripts refer to mains activation, cam-timer activation and solonoid valve s_1V activation respectively). $S_{1,2\text{ and }3}$ solonoids (Subscripts refer to S_1v, S_2v and S_3v respectively). $W_{1,2\text{ and }3}$ adjustable cams. $X_{1,2\text{ and }3}$ = cam operated microswitches.

The operation of the system is as follows: dried, charged neutralized aerosol enters the system at d at a rate of $q_{1,2}$ l min^{-1}. The inspiratory phase is characterised by aerosol passage along d (cam, w_1 down, to open x and close the 2-way valve s_1v; r_3 open) through g_1 and s_{2v} (w_2 up, to close x_2 and raise flap in s_{2v}) via i, to the dog. At the beginning of expiration, rotation of the cams, w, cause the switch positions at x_1 and x_2 to reverse simultaneously, this lowers the flap in s_{2v} to the expiratory position and opens s_1v. Aerosol is diverted to waste by the vacuum flow rate q_3 via the particle traps e and f. To ensure that all aerosol is diverted away from the animal during expiration, q_3 is adjusted to marginally exceed ($q_{1,2}$) such that a slight negative pressure (0.5–1.0 cm H_2O) may be recorded at g_2 with g_1 closed. The dog expires passively via k and s_{3v} into the plethysmograph balloon, m. Expired particulate material is retained in the expiratory pipework and the electrostatic precipitator, k, charged to an appropriate voltage (11 kV in the present study) by h. On inflation of the plethysmograph balloon, m, air is displaced from n, through the pneumatachograph head, o. The 3-way valve s_{3v}, is controlled by w_3 and x_3. During expiration s_{3v} links m with the dog. At the beginning of inspiration m is connected to a vacuum of sufficient flow (q_4) to enable complete evacuation of the plethysmograph balloon in one inspiratory phase.

Throughout aerosol administration a precalibrated pressure and flow meter linked to a twin pen recorder continuously monitors airway pressure at i and the expired volume at o. The meter converts the pressure differential across o to volume flow rate. This is then integrated with respect to time, to obtain a record of volume expired versus time. Mode control of the integration circuitry in p reinitialises the volume vs t record when flow from n through o ceases (end of expiration).

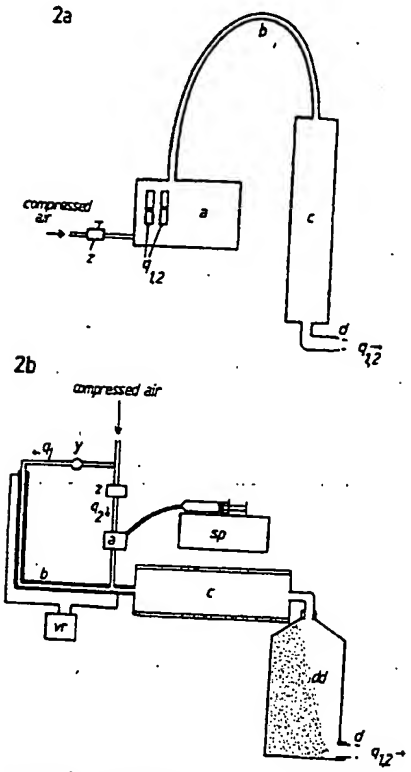


Fig. 2 Diagrammatic illustration of the apparatus used in conjunction with the administration system (Fig. 1) for aerosols produced (a) by a fluidised bed aerosol generator and (b) by a constant output nebulizer.

2a) Compressed air is delivered to the fluidised bed aerosol generator (a) at 40 psi via the pressure regulator (z). Total airflow ($q_{1,2}$) from the generator which consists of a flow (q_1) through the brass bead fluidised bed and a separate flow (q_2) to prevent brass bead contamination of the powder reservoir is adjusted as required. The substance to be aerosolized is placed in the powder reservoir from which it is carried by a bead chain to the fluidised bed. Aerosol leaves the generator via the arched tube (b) passes through the charge neutralizing column (c) and enters d of the administration system (Fig. 1).

2b) Compressed air is delivered to the nebulizer (a) at 35 psi via a pressure regulator (z). At this pressure the generator utilizes approximately 5 litres of air per minute (q_1). Total airflow ($q_{1,2}$) is adjusted as required using the dilution airflow (q_2) regulator (y). The solution to be aerolized is delivered to the nebulizer at a rate of 0.6 ml min^{-1} by a syringe pump (sp). Aerosol emerging from the generator mixes with the dilution air, passes through a jacketed charge neutralizing column (c) followed by a diffusion dryer (dd) and eventually enters d of the administration system (Fig. 1). All pipework for one metre prior to the confluence of the generator and dilution airstreams is clad in heating tape, (b) which is controlled by the voltage from a mains powered rheostat (vr) to raise the temperature of air entering c to 97 °C.

nebulizer [24] which produces aerosol droplets. In order that a direct comparison could be made between these different types of generator output, aerosols were charge neutralized by a ^{85}Kr radioactive source (Model 3050, Thermo Systems Inc., St. Paul, Minnesota/USA) and, where necessary dried prior to administration.

For aerosols produced by the fluidised bed generator the administration system was employed in conjunction with the apparatus shown in Fig. 2a, while for aerosols produced by the constant output nebulizer the system was used with the apparatus shown in Fig. 2b. With the exception of those components directly associated with aerosol generation, drying and charge neutraliza-

tion (everything to the left hand side of d, Fig. 1) the system used with both generators was identical. This ensured that aerosol sampling and administration methodology could remain constant irrespective of the generator employed.

Previous investigations had established that equilibration times of three hours and 10 minutes were required for the aerosol output concentration of the fluidised bed and constant output generators respectively to climb from zero to an effectively constant output (steady state). During this equilibrium period, prior to administration, aerosol was drawn to waste at 2 traps incorporated into the system (e and f Fig. 1: S_1v open by closing r_1 and r_3 with r_2 open).

Experimental protocol. Solid polydisperse disodium fluorescein aerosols (mass median aerodynamic diameter, MMD_{ae}, 1.1, 3.5 and 4.4 μm; geometric standard deviation, σg, 1.6, 1.3 and 1.3 respectively) were administered under the same respiratory regime by positive pressure ventilation to 2 adult male Beagle dogs (Body weight = 11.5 kg, both animals). Valve control electronics of the administration system were adjusted to give inspiratory and expiratory times of 1.95 and 5.9 seconds respectively and total airflow through the system set to 9.95 ($\pm$ 0.1) l min^{-1}. The two larger aerosols were produced by a fluidised bed generator (Fig. 2a) from jet-milled (Cavadell Ltd., East Peckham, Kent, U.K.) disodium fluorescein (Pure A.R. Koch Light Laboratories Ltd., Colnbrook, U.K.) previously dried for 72 hours at 70 °C. The 1.1 μm aerosol was generated by a constant output nebulizer (Fig. 2b) from aqueous disodium fluorescein solution (18.2 % w/v). Aerosol samples were obtained before and after administration for particle size analysis, using a cascade impactor (Model DC16, Delron Research Company, Powell, Ohio, USA) and concentration determination, according to the methods detailed in Clark and Byron [6].

Ninety minutes prior to surgery animals were sedated, 10 mg subcutaneous droperidol ("Droleptan", Janseen Pharmaceuticals Ltd., Martow, Bucks, U.K.) into the scuff of the neck. The left saphenous vein was cannulated (intravenous cannula set Type 200/500/030, Portex Ltd., Hythe, Kent, U.K., filled with 5 U ml^{-1} lithium heparin; The Boots Company Ltd., Nottingham, U.K., in 0.9 % w/v saline solution, "Polyfusor", The Boots Company Ltd.) and a further 10 mg droperidol followed by 8 ml 25 mg ml^{-1} sodium thiopentone ("Intraval" May and Baker Ltd., Dagenham Essex, U.K.) administered as separate intravenous boli. The animal was intubated (9.0 mm Magills endotracheal tube with inflatable cuff; McCarthys Surgical Division, Birmingham, U.K.) the endotracheal tube connected to the inspiration/expiration separator valve of the administration system (S_2v Fig. 1) and, with the valve in the inspiratory mode (flap in upper position see Fig. 1) and the sampling port, g_2, open (Fig. 1), the animal was allowed to respire normally through S_2v and g_2 while aerosol was diverted to waste (S_1v open, Fig. 1). Approximately one minute later sufficient i.v. sodium thiopentone (125 to 300 mg; the dose varies with animal) to cause complete respiratory depression was given, g_2 closed and aerosol administration initiated by closing r_2 and opening r_3 (see Fig. 1) simultaneously.

Administration lasted 14 to 21 minutes after which time autonomous respiratory control was regained by the animal. To prevent mucociliary clearance of aerosol to the gastro-intestinal tract the endotracheal tube was left in position until the animal would no longer tolerate its presence. Serial 3 ml blood samples were obtained during and for approximately 5 hours after administration for fluorescein determination. The amount of fluorescein absorbed was estimated as a function of time, t, from plasma concentration, C, versus time data according to Method II of Clark and Byron [6]. Intravenous control data required for this method was obtained from the same animals that had received aerosol using the same sedative, anaesthetic and ventilatory regimes as those employed during aerosol administration but differing in that ventilation employed aerosol free dry air. Animals were cannulated, an intravenous bolus dose of < 0.905 mg kg^{-1} fluorescein (the limit for linear pharmacokinetics: Clark et al. [7]) in 1 ml disodium fluorescein solution administered and serial blood samples obtained for fluorescein determination.

Assay of fluorescein. The concentrations and amounts of fluorescein throughout this article are expressed as equivalents of the anhydrous fluorescein dianion. The dianion content of all samples was determined spectrofluorimetrically.

Results

Polydisperse disodium fluorescein aerosols were administered under a controlled respiratory regime for up to 21 minutes, to 2 dogs using the apparatus shown in

Table 1 Characteristics of the solid, log-normally distributed, disodium fluorescein aerosol delivered to dog 1 and 2. The duration of ventilation (aerosol administration) in each experiment is also presented

Dog	MMD_{ae} (μm)	σg	Concentration (mg l^{-1})	Ventilation time (min sec)
1	1.0	1.6	0.098	16.00
2	1.1	1.6	0.097	20.11
1	3.6	1.2	0.119	14.04
2	3.4	1.3	0.110	18.00
1	4.5	1.3	0.169	20.10
2	4.4	1.3	0.183	21.20

Fig. 1. During administration, total airflow was 9.95 ± 0.1 l min^{-1} (Mean ± S.D., n = 6) and peak inspiratory pressures, measured in the endotracheal tube, ranged 10.5 to 12.0 cm H_2O. Inspiratory and expiratory times were 1.95 and 5.9 sec respectively; inspired tidal volume averaged 264.4 ± 10.5 ml in all experiments except that involving 1.0 μm MMD_{ae} aerosol administration to dog 1, when the inspiratory time was slightly shorter, 1.93 sec, and inspired tidal volume averaged 220 ml.

Both animals received similar aerosols in terms of concentration and particle size distribution. All aerosols were log-normally distributed. Values for aerosol concentration, MMD_{ae} and σg are shown in Table 1 together with the duration of administration on each occasion.

Fractional deposition of the different aerosols within the Beagle respiratory tract and the inspiratory and expiratory sides of the administration system, following

Table 2 Fractional deposition of the aerosol within the respiratory tract (dogs 1 and 2) and the inspiratory and expiratory sides of the administration system

Dog	MMD_{ae} (μm)	Fractional Deposition		
		Inspiratory losses	Absorbed via respiratory tract	Exhaled
1	1.0	0.025	0.322	0.653
2	1.1	0.029	0.402	0.569
1	3.6	0.189	0.616	0.195
2	3.4	0.216	0.592	0.192
1	4.5	0.479	0.447	0.074
2	4.4	0.452	0.456	0.092

Table 3 Bioavailable fluorescein dose following the administration of three different disodium fluorescein aerosols under the same respiratory regime to dogs 1 and 2

MMD_{ae} (μm)	Bioavailable dose (mg)	
	Dog 1	Dog 2
1.1	0.64	1.25
3.5	1.41	2.75
4.4	2.95	4.03

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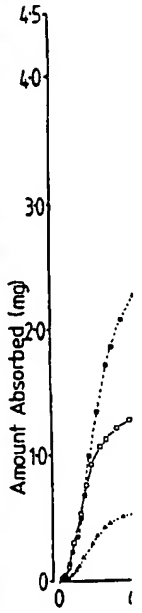

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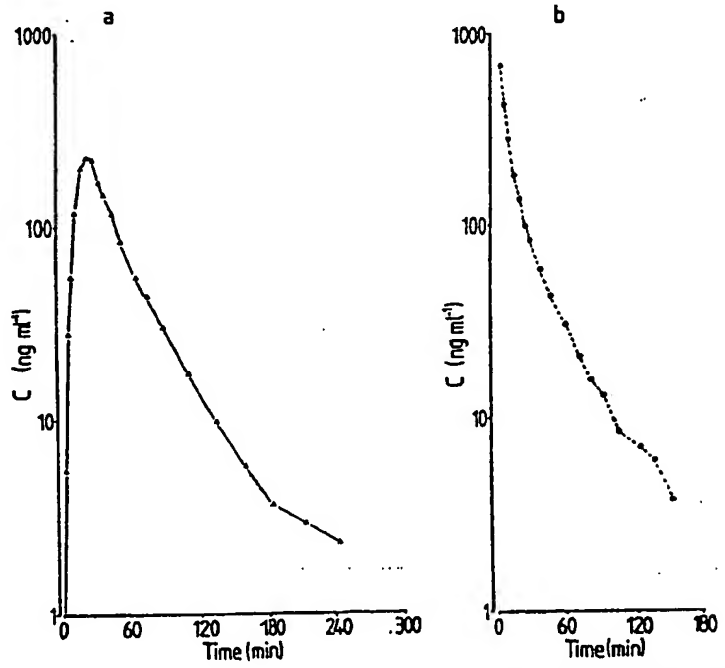

Fig. 3a and b Typical plasma fluorescein concentration versus time profiles following a) aerosol and b) intravenous bolus administration of disodium fluorescein. Both sets of data were obtained from Dog 1. Aerosol (3.6 μm MMD_{ae}) administration (a) commenced at t = 0 and finished at t = 14 min 4 sec. The intravenous fluorescein dose (b) was 1.513 mg.

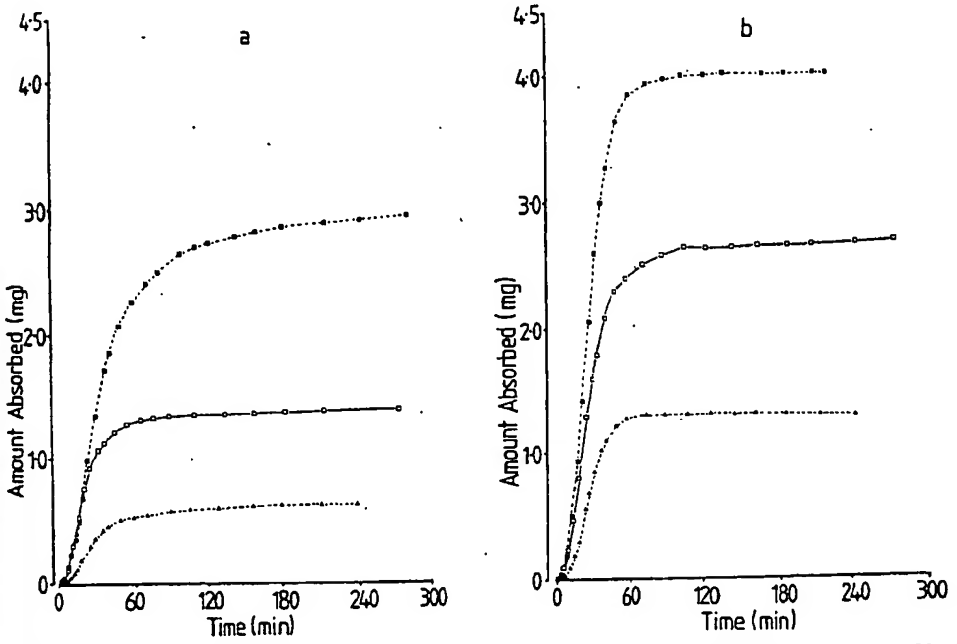

Fig. 4a and b Fluorescein absorption versus time profiles determined according to Clark and Byron (1985) following the administration of 1.1 (▲·····▲), 3.5 (□——□) and 4.4 (■ ····· ■) μm MMD_{ae} disodium fluorescein aerosols to dog 1 (Fig. 4a) and dog 2 (Fig. 4b). Administration commenced at t = 0 in all cases.

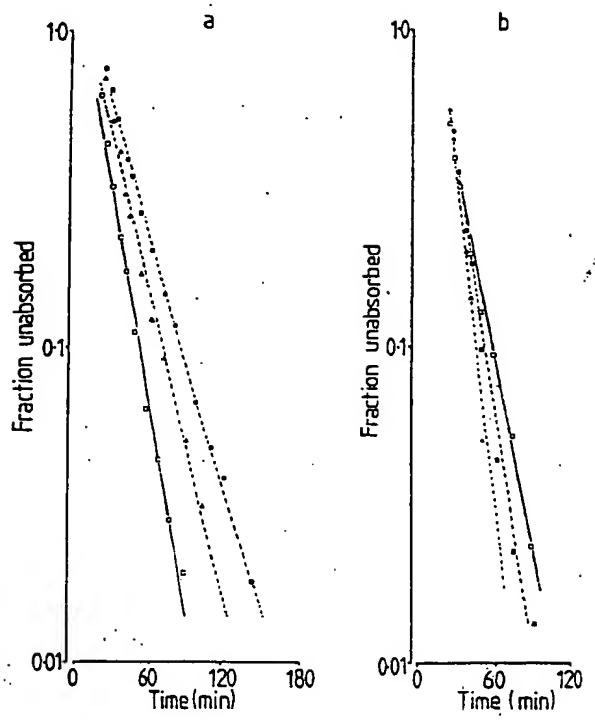

Fig. 5a and b Fraction unabsorbed f, versus time after the end of administration of 1.1 (▲·····▲) 3.5 (□——□) and 4.4 (▩·····▩) μm MMD_{ae} disodium fluorescein aerosols to dog 1 (Fig. 5a) and dog 2 (Fig. 5b). The straight lines are best fits to the experimental data determined by least mean squares regression analyses. Administration commenced at t = 0 in all cases.

ventilation, are shown in Table 2. Results obtained from both animals were in close agreement. Inspiratory losses and the amount expired were determined by washing the system between g_1 and k (Fig. 1) and assaying washings for fluorescein content. Dose retained within the respiratory tract was determined from the amount absorbed, assuming that fluorescein was totally available from the tract subsequent to its administration as the disodium salt [6]. As aerosol particle size increased, a smaller fraction was exhaled and a larger proportion deposited on the inspiratory side of the system. Although maximum fractional deposition within the respiratory tract occurred with the 3.5 μm MMD_{ae} aerosol (Table 2), a greater mass of fluorescein was retained with the 4.4 μm aerosol (Table 3) due to its greater concentration (Table 1) and increased administration period.

Typical plasma fluorescein concentration versus time profiles after aerosol and intravenous disodium fluorescein administration are shown in Fig. 3a and b respectively. Intravenous control experiments provided triexponential C vs t curves in both animals. Fluorescein absorption versus time profiles obtained (Clark and Byron [6]) from C vs t data following the administration of 3 different aerosols to dog 1 and 2 are shown in Fig. 4a and b respectively. In all cases as $t \to \infty$ the amount absorbed, A, tended towards the bioavailable dose (Table 3) calculated [7] by comparison of areas under the i.v. and aerosol C vs t profiles. In both animals the rate of fluorescein absorption (mg min^{-1}, Fig. 4a and b), after aerosol adminis-

Table 4 First-order absorption rate constants following the administration of 3 different disodium fluorescein aerosols to dog 1 and 2

MMD_{ae} (μm)	Absorption Rate Constant (min^{-1})	
	Dog 1	Dog 2
1.1	0.036	0.065
3.5	0.042	0.047
4.4	0.030	0.058

tration was complete (Table 1) tended to increase proportionally with the amount deposited (bioavailable dose, Table 3).

Fig. 5a and b are semilogarithmic plots of fraction, of fluorescein unabsorbed, f, versus time following the end of administration (Table 1) for all 3 aerosols delivered to dog 1 and 2 respectively.

Data for each aerosol was apparently rectilinear, suggesting first-order kinetics for fluorescein absorption from the lung by an non-saturable process such as simple diffusion. Values for the apparent first order rate constants, k, determined by linear regression analysis of the data in Fig. 5a and b are summarised in Table 4. Absorption half lives (0.693/k) averaged 11.4 and 17.3 min^{-1} in dog 1 and 2 respectively.

Discussion

In order to determine the effect of particulate characteristics and respiratory variables upon the absorption of compounds delivered as inhalation aerosols, it is necessary to deliver well characterised aerosols in a highly controlled manner. The system (Fig. 1) detailed above enabled disodium fluorescein aerosols to be delivered by controlled ventilation to the respiratory depressed Beagle. The administered aerosol may be varied by changing the generator or the material from which the aerosol is produced and the respiratory regime altered by varying inspiratory/expiratory times and airflow through the system. The respiratory regime employed in the present study (respiratory rate 7.64 respirations min^{-1}, tidal volume $\sim$264 ml) was chosen to satisfy the respiratory requirements of the anaesthetised Beagle. For animals of the size used in this study, minute volumes of 2.0 litres have been reported [10].

As aerosol particle size increased, a smaller fraction was exhaled and a larger proportion deposited on the inspiratory side of the administration system. Maximum fractional deposition in the Beagle respiratory tract was observed with the 3.5 μm MMD_{ae} aerosol. Previous studies [6] have shown that following aerosol administration using the system illustrated in Fig. 1, the dose deposited in the respiratory tract cannot be determined accurately by mass balance i.e. (Volume inspired $\times$ inspired aerosol concentration) – amount exhaled – amount lost. This is due to difficulties in measuring inspired aerosol concentrations during positive pressure administration which differ from concentrations determined when the system is not pressurised. Problems of this nature are well recognised in the aerosol literature. A disparity between the theoretical and actual amounts within the respiratory tract has been observed by Kreyling and co-workers [21]. However, because fluorescein is totally absorbed from the respiratory tract following administration as its disodium salt [7] the deposited dose of this compound may be calculated from the area under the C vs t profile.

Whether particulate deposition is governed by impaction or sedimentation, the larger the particle, the earlier it will deposit in a system such as the one illustrated in Fig. 1. Because regional aerosol deposition within the respiratory tract is known to be a function of aerosol particle size [23] administration of these three different aerosols (Table 1), under an effectively constant regime, probably results in different deposition patterns.

Semilogarithmic plots of fraction of fluorescein dose unabsorbed versus time following the end of aerosol administration were apparently linear for all aerosols administered (Fig. 5a and b). This together with the direct increase in the rate of absorption (mg min^{-1} Fig. 4a and b) with dose, for the range of doses administered indicated apparent first-order absorption of fluorescein from the respiratory tract by a non-saturable process such as simple diffusion. A saturable carrier transport mechanism for another anionic dye, phenol red, has been demonstrated in rat lung [14] and similar mechanism are known to exist for fluorescein in other parts of the body [2, 3]. However, for fluorescein aerosol doses <4.03 mg administered over some 20 minutes we found no evidence for carrier mediated transport in canine lung.

Despite efforts to maintain identical conditions in all experiments some intra-animal variation in absorption rate constant must be expected due to variations in fluorescein clearance between experiments. Absorption rate constant, k (min^{-1}) values obtained for both animals differed slightly between experiments but appeared unrelated to aerosol particle size (Table 4). Aerosol particle size and presumably therefore regional deposition seemed to have little or no effect on these values.

At physiologic *p*H, disodium fluorescein is very water soluble, existing, in solution, predominantly as the dianion [6]. For the aerosol particle sizes investigated, dissolution of the disodium salt in respiratory tract fluid should be extremely rapid and much faster than absorption. During its transference from the airway to the systemic circulation a solute must pass through a number of barriers of which the pulmonary epithelium is believed to provide most resistance to passage [9]. Lipophobic compounds, such as fluorescein, traverse this barrier primarily via intercellular pores, at rates that are dependent upon their molecular weight [11, 13, 27] and independent of pulmonary blood flow rates.

Given the existence of diffusion barrier control, first-order transport constants (k), are theoretically dependent upon barrier permeability, P, and an area to volume ration, A/V, as

$$k = P(A/V) \qquad \text{(Eq. 1)}$$

where P is the ratio of the product of solute diffusion coefficient, D, in the barrier and solute (barrier/donor solution) partition coefficient, K, to barrier thickness, h, ($P = DK/h$), A is the area through which diffusion occurs and V is the solution volume from which the solute diffuses [5, 11]. Because the A/V ratio is believed to remain effectively constant in different regions of the respiratory tract [11] the observation that k was effectively independent of particle size and to some extent regional deposition (Table 4), following disodium fluorescein aerosol administration direct to the canine lung, indicates that the permeability of the rate controlling barrier remains constant in different lung regions. Alternatively, the bulk of the deposition may be relatively insensitive to aerosol size.

Conclusions

Aerosol particle size and, to some extent, regional deposition within the respiratory tract appeared to have no effect on the absorption rate constant for disodium fluorescein.

Aerosol administration of this compound and measurement of resultant concentration versus time profiles may provide a valuable means of estimating pulmonary epithelial permeability without the use of radioisotopes. It appears from the present study that even water soluble compounds like fluorescein (molecular weight of the dianion = 330) which exists in a totally ionised form at physiologic *p*H, are probably cleared from the canine lung via systemic absorption, with half-lives around 15 minutes. Therapeutic inhalation aerosols designed for local drug delivery to the human respiratory tract could perhaps usefully employ controlled release technology in order to sustain desired pharmacologic effects, while others, containing compounds for systemic activity, may utilise this route of drug delivery for rapid input.

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Buchbesprechung

Mucosal Immunity. Hrsg. GALLIN, J. I.; FAUCI, A. S. 208 S. mit 26 Abb. und 9 Tab., 15,5×24 cm. New York: Raven Press 1985 (Advances in Host Defense Mechanism, Vol. 4). Geb., Leinen, $ 47.00.

Die meisten Erreger von Infektionskrankheiten dringen über den Respirations-, Gastrointestinal- oder Genitaltrakt in den menschlichen Organismus ein. Mehr Information über die Immunmechanismen dieser Schleimhäute erscheint daher für viele Ärzte und Naturwissenschaftler wichtig.
Das vorliegende Buch ist eine sehr gute Zusammenfassung der experimentellen und klinischen Forschungsergebnisse der letzten Jahre auf dem Gebiet der Schleimhautimmunologie. Durch eine gut durchdachte und differenzierte Gliederung ist es gelungen, die verschiedenen lokalen immunologischen Abwehrprozesse (humorale und zelluläre) sowie deren Wirkungsweise bei der Abwehr von Infektionen des Respirations- und Gastrointestinaltrakts übersichtlich abzuhandeln.
In einem eigenen Kapitel werden Erkenntnisse der Grundlagenforschung bezüglich der Zelldifferenzierung, Migration und Funktion des mukosaassoziierten Immunsystems dargestellt, was von großer Bedeutung für das generelle Verständnis der folgenden Kapitel ist. Es ist den Autoren gelungen, unnötige Wiederholungen in den Kapiteln des Buches zu vermeiden, obwohl die einzelnen Kapitel von verschiedenen Fachspezialisten geschrieben wurden.
Das Buch ist durch zahlreiche Tabellen und Abbildungen gut illustriert und enthält detaillierte methodische Beschreibungen sowie ein sehr umfangreiches Literaturverzeichnis mit einer Vielzahl neuester Arbeiten auf dem Gebiet der Erforschung lokaler immunologischer Prozesse, was für den experimentell tätigen Wissenschaftler von hohem Wert ist.

HARTMUT TISCHNER (Berlin-Buch)

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1/1 - (C) BIOSIS / BIOSIS XP-002214728
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AU - KNIGHT V; BLOOM K; WILSON S Z; WILSON R K
AUAF- DEP. MICROBIOL. IMMUNOL., BAYLOR COLL. MED., HOUSTON, TEX. 77030, USA
DT - Article
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16506-22003-22005 22030-22100 25504 33502 33506 36006-38506*
XNPL- 0066-4804-16-5-572
AB - Seven well volunteers and 3 patients with a naturally occurring influenza A/USSR/77 (H1N1)-like infection were given amantadine by small-particle aerosol with a Collison generator modified for this purpose. Inhalation periods for the volunteers were increased on consecutive weekends from 15 min to 1 h, 4 h, 9 h and 2 consecutive days of 6 h each. The particle size was 1.2-.mu.m mass median diamete and the concentration of inhaled aerosol ranged 47-75 .mu.g/l. Estimates of retained doses in 9 h were 74-149 mg. About 2/3 of the dose was recovered in the urine. Pulmonary function studies did not vary significantly from base-line values and were within a normal range for 5 of 7 volunteers. Two volunteers with a moderate reductio in mid-maximal flow before exposure had a total of 3 episodes of coughing and wheezing associated with moderate reductions in mid-maximal flow values. These episodes cleared spontaneously or improved promptly after isoproterenol therapy. The patients with influenza tolerated the treatment well and recovered promptly.
AW - ** Miscellaneous Descriptors **
HUMAN INFLUENZA VIRUS ANTIVIRAL-DRUG INFLUENZA INFECTION DOSAGE PULMONARY FUNCTION THERAPY
NR - 5
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PG - 572-578
PUB - Antimicrobial Agents and Chemotherapy
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TI - AMANTADINE AEROSOL IN HUMANS
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AN - PREV198069008137
AU - WILSON S Z; KNIGHT V; MOORE R; LARSON E W
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TEX. 77030, USA.
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13002-16001-22002-22030-22100 33506 36006-38506*
XNPL- 0037-9727-161-3-350
AB - An aerosol generator suitable for administration of a small-particle aerosol of amantadine for treatment of influenza A infection in man described. As currently operated, the usual daily recommended oral dose of amantadine of 120-200 mg can be given in 8-10 h of inhalatio of the aerosol. Limited clinical study indicates the safety and probable efficacy of the treatment method.
AW - ** Miscellaneous Descriptors **
HUMAN ANTIVIRAL-DRUG INFLUENZA A INFECTION
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TI - AMANTADINE SMALL PARTICLE AEROSOL GENERATION AND DELIVERY TO MAN
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